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Post Stroke Depression and Emotional Incontinence : Focused on TPH2 Polymorphisms

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고 미 혜

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Abstract

Post Stroke Depression and Emotional Incontinence : Focused on TPH2 Polymorphisms

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Stroke survivors often have chronic disabilities such as motor dysfunction, sensory dysfunction, dysarthria and ataxia. Post stroke emotional dysfunction (PSED) including post stroke depression (PSD) and emotional incontinence (PSEI) has been also reported

to be common in these patients. It is necessary to understand the risk factors associated with PSD and PSEI.

The aim of this study was to identify the general, clinical and genetic characteristics of patient at 3 months post stroke and factors associated with to PSD and PSEI at 3 months after stroke. Specifically, the present study was to investigate the association between different genetic variants of the TPH2 gene and PSD as well as PSEI at 3 months after stroke.

This study was a secondary analysis from the primary study (S Choi-Kwon et el., 2012). A total of 383 patients who were followed at 3 months were finally included in the descriptive study. They were recruited from Asan Medical Center in Korea with a diagnosis of acute stroke. Collection of demographic and clinical data and assessment of PSD and PSEI and DNA analysis were performed. The data were analyzed with χ2-test, Fisher's exact test, and Multiple Regression Analysis, using SPSS (version 21.0).

The results of the study were as follows:

1) Eighteen % (n=69) of the post stroke patients were PSD and eleven % (n=42) of the subjects were PSEI at 3 months after stroke.

2) No differences in the rs10879355 were observed between the patients with and without PSD and PSEI. However, the genotype frequencies of rs4641528 differed significantly 3months post stroke between the patients with and without PSD (p= .015) and PSEI (p= .40).

3) PSD was significantly different by motor dysfunction (p< .05), sensory dysfunction (p< .05), dysarthria (p< .05), high NIHSS score at admission (p< .01), mRs at admission (p< .05), and mRs after 3months (p< .01).

4) PSEI was significantly different by lesion location (p< .05), high NIHSS score at admission (p< .01), and mRs after 3months (p< .01).

5) In a stepwise multiple regression analysis including age, gender, and factors in univariate analysis (p< .05), the NIHSS score (β = .123) and mRs at 3 months (β =1.181) were associated with PSD.

6) In a stepwise multiple regression analysis including age, gender, and factors in univariate analysis (p< .05), rs4641528 (TPH2 SNPs) (β =1.706) and the NIHSS score (β = .154) were associated with PSEI.

The results of the study demonstrated the contributions from both genetic factors and physical dysfunction interacting in the development of PSD and PSEI at 3 months post stroke. This study in nursing practice may also contribute to the understanding of disease risks and its influence on disease management.

keywords : stroke, post stroke depression, post stroke emotional incontinence, TPH2 polymorphism

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I. Introduction

1. Background

Stroke is the second leading cause of death based on the annual incidence rate by the Korean Statistical Information Service (KOSIS). Stroke survivors often have chronic disabilities such as motor dysfunction, sensory dysfunction, dysarthria and ataxia depending on the lesion location (Clerici, 2013). Post stroke emotional dysfunction (PSED) including post stroke depression (PSD) and emotional incontinence (PSEI) has been also reported to be common in these patients (Jong S Kim, Choi, Kwon, & Seo, 2002). These emotional changes have been shown to decrease the quality of life (QOL) of patients and increase mortality (Smi Choi-Kwon, Choi, Kwon, Kang, & Kim, 2006). In addition, it negatively affects the will of patients during rehabilitation and places a burden on care give (Srivastava, Taly, Gupta, & Murali, 2010).

PSD and PSEI, however, are complex disorders and related factors yet to be discovered. Previous studies reported that neurological dysfunction and lesion location are factors associated with PSD and PSEI (Jong S Kim & Choi-Kwon, 2000).

Serotonin (5-hydroxytryptophan, 5-HT) dysfunction has been also implicated in the etiology of PSD (Whyte & Mulsant, 2002). Moreover pharmacological studies suggest that alterations in the serotonin neurotransmitter system play an important role in PSD and PSEI (Hackett, Yang, Anderson, Horrocks, & House, 2010). The contribution of the 5-HTT gene toward the development of PSD has been also demonstrated in Western countries (Bozina, Mihaljevic Peles, Sagud, Bilusic, & Jakovljevic, 2008) and in Korea (S Choi-Kwon et al., 2012).

Tryptophan hydroxylase 2 (TPH2) gene which is a rate-limiting enzyme gene in the biosynthesis of serotonin in the brain is another candidate gene with relation to PSD and PSEI. Previous studies indicated that TPH2 is related to anger proneness or depressive symptoms in psychiatric patients (Jaewon et al., 2010; Zill et al., 2004). The relationship between the TPH2 gene and PSD and PSEI, however, has yet to be determined.

It is reasonable, therefore, to hypothesize that the tryptophan hydroxylase (TPH) 2 gene may be one of the candidate genes associated with PSD and PSEI. The goal of the present study was to investigate the association between different

genetic variants of the TPH2 gene and PSD as well as PSEI at 3 months after stroke. Moreover, we attempted to investigate how important these genetic predispositions are to the development of PSD and PSEI at 3 months post stroke along with other neurological and organic factors.

Understanding PSD and PSEI with associated factors among stroke patients could be quite an importance in screening the high risk patients and their treatment. This genetic association study in nursing practice may also contribute to the understanding of disease risks and its influence on disease management. Moreover, it will enhance the ability of nurses to provide genetic counseling the patients and their families (Greco & Salveson, 2009).

2. Purpose

The purpose of this study was to identify factors associated PSD and PSEI. The specific aims of this study were as follows.

1) To identify the general, clinical and genetic characteristics of patients at 3 months post stroke
2) To identify the prevalence of PSD and PSEI at 3 months after stroke
3) To identify the relationships between different genetic variants of the TPH2 SNP and PSD and PSEI at 3 months post stroke
4) To identify the predictors of PSD and PSEI at 3 months post stroke including neurological, functional, and genetic factors.

3. Definition of terms

1) Post stroke depression

Post stroke depression was defined as mood disorders contributed to a general medical condition in which post stroke patients exhibited tearfulness, a depressed mood and feelings of hopelessness caused by pathological mood swings. In this study, PSD was defined if the patients scored below 14 in the 21-item Beck Depression Inventory (BDI) (Beck, Steer, & Brown, 1993) (S Choi-Kwon et al., 2012).

2) Post stroke emotional incontinence

Post stroke emotional incontinence is one of emotional disturbances patients can suffer from post stroke. In this study, the definition by J.S. Kim (2005) was used where post stroke patients reported more than 2 episodes of uncontrollable laughter, crying or both for no evident reason.

II. Literature Review

I. PSD and PSEI

1) Introduction of PSD AND PSEI

Stroke is a major health problem in the elderly population of the Aepublic of Korea. Based on the annual incidence rate by the Korean Statistical Information Service (KOSIS), stroke is the second most common cause of death after cancer. There has been a gradual, continuous decline in mortality. This has resulted in increasing numbers of survivors. This means that a majority of post stroke patients left with physical and mental impairments as well as disabilities in activities of daily living.

From previous research on post stroke patients, most stroke survivors have physical and mental disabilities (Ahlsio, Britton, Murray, & Theorell, 1984; King, 1996). A study by King (1996) reported that predictors of quality of life after stroke are depression, social support, and functional status. Among them, emotional disturbances like depression often follow a stroke. The reported prevalence for emotional disturbances vary widely from less than 25% to more than 60% (Astrom, 1996). Mood disorders occurring after stroke are a major public health because they occur frequently and are difficult to diagnose and treat (Carota & Bogousslavsky, 2012).

Herrmann (1998) explained that post Stroke depression affects the recovery of patient' s. the effectiveness of rehabilitation was reduced because of symptoms of depression (Gillen, Tennen, McKee, Gernert-Dott, & Affleck, 2001). Furthermore, depression and other mental health diagnoses after stroke increased inpatient and outpatient medical utilization three years post stroke (Ghose, Williams, & Swindle, 2005).

Post stroke depression is a leading cause of death and frequently reduces the patient' s quality of life (QOL) even with survival (Smi Choi-Kwon et al., 2006). PSD can be distressing for both patients and their caregivers, increasing the burden on caregivers (Gbiri, Akinpelu, & Odole, 2010). However, Akinpelu & Gbiri (2008) reported that post stroke depression had a weak impact on quality of life (QOL).

Another psychological sequelae, post stroke emotional incontinence affects 11~52% of all stroke survivors (Tang et al., 2009). It is also a distressing and embarrassing complaint because the patient is often socially disabled which could

interfere with rehabilitation (Grethe Andersen, Vestergaard, & Riis, 1993).

Post stroke depression (PSD) and Post stroke emotional incontinence (PSEI) are common emotional dysfunction (Hackett et al., 2010). These two emotional dysfunctions are closely related. However, most patients with PSEI do not have depression. According to Kim (2000), development of PSD and PSEI is strongly influenced by the lesion location which is quiet distinct because of its association with different anatomical locations. PSEI is more associated with to lenticulocapsular strokes than that of PSD.

2) Associated factors of PSD and PSEI

In this section, previous studies were reviewed to determine what factors are associated PSD and PSEI.

There have been a lot more studies on PSD than on PSEI. Despite intensive research, there is still significant controversy over the risk factors of PSD. Probably there are at least two aspects to the mechanism of post stroke depression. One view is that, the lesion location itself acts as a neurotransmitter which is associated with PSD (Robinson et al., 2000). The other view is that PSD occurs because of the social, psychological, and physiological stresses associated with stroke

Factors that have been identified as being associated with PSD in previous studies were demographics, lesion location, size, activities of daily living (ADL) and changes in family role. General characteristic such as age and gender have not been shown to have an association with PSD, and the decreased ADL due to physical disability has been shown to be one of the main factors of PSD in many studies (G. Andersen, Vestergaard, Ingemann Nielsen, & Lauritzen, 1995; Gottlieb, Salagnik, Kipnis, & Brill, 2002; N. Herrmann, S. Black, J. Lawrence, C. Szekely, & J. Szalai, 1998). Among the studies on PSD, there have been no consistent findings showing an association between lesion location and size with PSD (S. J. Kim et al., 2005). Fuentes et el. (2009) reported that lesion location and size could not fully explain the onset of PSD.

However, lesion location is the most relevant factor of PSEI. Previous studies showed that lenticulocapsular strokes are closely associated with PSEI (Jong S Kim, 2002).

Over the last two decades, research on post stroke depression has focused on the assessment of lesion location, and psychosocial and demographic risk factors as determinants of PSD (Whyte & Mulsant, 2002). In recent years, molecular genetics approaches have been widely used to investigate biological mechanisms that contribute to interindividual differences in susceptibility to primary psychiatric disorders (Rajamannar RamasubbuRose Tobias, Buchan, & Bech-Hansen, 2006).

It has increasingly been shown that primary major depression (major depression not due to a medical condition) results from the interaction of predisposing genes and a hazardous environment. Major depression can be caused by an inappropriate secretion of serotonin, a neurotransmitter (Owens & Nemeroff, 1994). In modern medicine, symptoms of depression can be improved by taking SSRIs (selective serotonin reuptake inhibitors) which modulate serotonergic function in the body. However, the genetic hypothesis for PSD and PSEI has not been investigated to date (G. Andersen et al., 1995). Therefore, serotonin-related genes are good candidates to study of PSD and PSEI.

According to a review of the literature, it is important to understand the risk factors associated with PSD and PSEI. Molecular genetics approaches, as mentioned earlier, are needed in this area. Genetic factors have come into the spotlight recently. So, a review of the literature for serotonin related genes needs further consideration.

2. TPH2 SNPs

1) Serotonin related gene polymorphisms

Polymorphisms have been identified in a large number of genes that could influence behavior. Most often, the DNA variant evaluated in genetic association studies is a single nucleotide polymorphism (SNP), which is defined as a single base change occurring in the population at a frequency greater than or equal to 1%.

The disturbance of the serotonergic system has been implicated in the etiology of depression. A number of candidate genes involving serotonin metabolism and serotonergic transmission have been investigated.

Serotonin related genes that modulate the functions of the neurotransmitter serotonin function are organized into three

functional groups. The first group is involved in the synthesis process, the second group in the transport process and the third group in the reception process. Several of the genes involved in the functions of serotonin exhibit genetic variations. These include serotonin receptors, enzymes (Tryptophan hydroxylase and monoamine oxidase A) and serotonin transporters. Variants of the serotonin transporter gene, 5-HTTLPR (5-HT transporter linked polymorphic region) and STin2 VNTR (a variable number of tandem repeat in the second intron), are associated with susceptibility to major depression (Rajamannar RamasubbuRose Tobias et al., 2006). Another mutation introduces non-sense codons as seen in the monoamine oxidase A mutation found in a Dutch kindred resulting in a truncated peptide (Sabol, Hu, & Hamer, 1998). This X-linked mutation results in a behavioral syndrome in males (Kim-Cohen et al., 2006). TPH is the rate-limiting enzyme in the biosynthesis of serotonin. Variants in the TPH gene could influence serotonin turnover (Nielsen, Dean, & Goldman, 1992).

2) TPH2 SNPs

Tryptophan hydroxylase (TPH) is a rate limiting enzyme involved in the biosynthesis of serotonin. TPH catalyzes the biopterin-dependent monooxygenation of tryptophan to 5-hydroxytryptophan, which subsequently is decarboxylated to form serotonin. Two TPH isoforms have been identified.

Human TPH1 and TPH2 are expressed in nearly equal amounts in several brain regions (frontal cortex, thalamus, hippocampus, hypothalamus and amygdale), with a predominant expression of TPH2 in the brain stem, which is the major locus of the serotonin-producing neurons, whereas TPH1 mRNA is exclusively present in peripheral tissues such as the heart, lung, kidney, duodenum, liver and adrenal gland (Zill et al., 2004). Therefore, it appears that the TPH2 gene is more pertinent in the genetics of mood regulation.

TPH1 SNPs were shown to be associated with depression and its response to treatment in Caucasian populations (Serretti et al., 2001). Peters et el. (2004) also found some positive associations in the SNPs of the TPH1 gene with antidepressant activity. However, there have been no consistent findings concerning the relationship between TPH1 SNPs and depression as well as therapeutic response in Asian populations (Ham et al., 2004; Yoshida et al., 2002). The results of these studies

showed ethnic differences.

Furthermore, some SNPs and haplotype studies have investigated associations for the TPH2 gene; some found a positive association between the TPH2 gene and depression (Xinhua et al., 2011; Zill et al., 2004), anger (Jaewon et al., 2010), bipolar disorder (Choi, Yoon, & Kim, 2010), ADHD (Shim et al., 2010), and suicidal behavior (Yoon & Kim, 2009), whereas others did not (Mouri et al., 2009). Despite the many previous studies, there are no studies on the association between the TPH2 gene and depression after stroke (post stroke depression). Considering the above mentioned findings, the TPH2 gene represents a new and interesting candidate gene for PSD and PSEI, not yet investigated.

Therefore, the aim of this study was to identify factors associated with to PSD and PSEI at 3 months after stroke. As described above, there is accumulating evidence pointing toward a role for the serotonin system in PSD and PSEI. We also investigated the association of different genetic variants of the TPH2 SNPs with PSD and PSEI.

III. Methodology

1. Study Design

This was a prospective descriptive study on stroke patients at 3 months post stroke. This study was a secondary analysis from the primary study (S Choi-Kwon et al., 2012). Specifically, this analysis examined the association between post stroke emotional dysfunction and Tryptophan hydroxylase 2 gene.

2. Subjects

A total of 508 participants were recruited from Asan Medical Center in Korea with a diagnosis of acute stroke between March 2008 and February 2010 in the primary study (S Choi-Kwon et al., 2012). All subjects were recruited during admission. CT or MRI scan of the brain was performed within 7 days after stroke onset.

For the purposes of this study, the following patients were excluded; those who 1)did not undergo imaging (CT/MRI) studies, 2) had an intracerebral hemorrhage, subarachnoid hemorrhage, arteriovenous malformation, venous infarction, or moyamoya disease(N Herrmann et al., 1998), 3) had transient ischemic attack without progression to stroke, 4) had communication problems(aphasia, dementia, or dysarthria) severe enough to prevent them from undergoing a reliable interview, 5) scored $\leq$ 23 on the Mini mental state examination, 6) had a history of being diagnosed with depression or other psychiatric illnesses prior to the onset of stroke, 7) had been receiving serotonin reuptake inhibitors (SSRIs) for any reason, 8) lived alone making information from relatives un-available, and 9) did not give written consent.

After 3 months, 39 patients were lost from follow-up because of their physical or cognitive condition, refusal, and death (S Choi-Kwon et al., 2012). Eighty-six patients were also excluded from the secondary analysis because of insufficient amount of DNA sample during DNA genotyping. Thus, 383 patients were finally included in the secondary analysis. There were no significant differences in general and clinical characteristics between the patients who were followed at 3 months (n=383) and who were excluded in the secondary analysis (n=86).

3. Measurements

1) Demographic and clinical data

This research collected the following data; demographics (age, sex, and educational level), vascular risk factors (history of smoking, drinking, hypertension, diabetes mellitus, cardiovascular disease, hyperlipidemia, and stroke), locations of lesions, functional level(motor dysfunction, sensory dysfunction, dysarthria, and ataxia), features of the index stroke(modified Rankin scale, mRs) and stroke severity based on the National Institute of Health Stroke Scale (NIHSS) (Tang

et al., 2004).

2) Measurement of post stroke emotional dysfunction(PSED)

(1) *Post stroke depression*

The presence of PSD was assessed with the BDI (Beck Depression Inventory) translated by Lee and Song (Lee & Song, 1991). The BDI consists of 21 questions with a likert scale of 4. Total scores range from 0 to 63. Patients with score less than14 was considered to have PSD. In this study, the Cronbach's α was .87.

(2) *Post stroke emotional incontinence*

Post stroke emotional incontinence is defined as virtually uncontrollable episodes of laugher (EIL), crying (EIC), or both. For PSEI, patients and relatives were asked if the patient showed excessive and/or inappropriate laughing (EIL), crying (EIC), or both compared with the pre-morbid state. When both agreed that the patient exhibited one or the other or both EIL and EIC at least on 2 separate occasions, that patient was considered as having PSEI. 'Inappropriateness' indicates laughing or crying that occurs while talking, listening, meeting people or watching TV, which is not particularly amusing or sad to ordinary people (Jong S Kim & Choi-Kwon, 2000).

3) TPH2 gene

(1) *Selection of TPH2 SNPs*

Because studying every SNP in the human genome is not cost-effective with current microarray technology, DNA analysis employ a subset of SNPs called tag SNPs. Using tag SNPs allows the investigator to maximize information content and minimize sample size without losing the power to detect genetic association. More than 2.2 million common SNPs (minor

allele frequency ≥ 5%) in four ethnic groups (Caucasians in Utah, Han Chinese in Beijing, Japanese in Tokyo, and Yoruba in Ibadan, Negiria) were genotyped as part of the international HapMap Project. From this data set, we selected the SNPs with the optimal minor allele frequency and the best genomic coverage to serve as tag SNPs for each population.

So, we consulted the HapMap database (Hapmap data base 3/Rel #2, Feb 09) and captured thirteen SNPs. Among them, we selected two tagging SNPs (rs4641528, rs10879355) covering the TPH2 gene with the criteria of an r^2 threshold greater than 0.8 in 'pair-wise tagging only' mode using the 'Tagger' program, an implement of the Haploview software for the association analysis. The mean max r^2 of the two SNPs was .953.

(2) *SNPs genotyping*

DNA was extracted from peripheral blood collected at admission using a QIAamp DNA mini Kit (Qiagen Inc, USA) and stored in a -70 ℃ freezer. We selected two SNPs (rs4641528, rs10879355). Polymerase Chain Reaction (PCR) was performed with the following primers; F 5' - AAA GAT ACC TGT CTT TTG CTC ACT TT-3' , R 5' -CTG GCT CCA AAT GAA AGC TCA GGC A-3' (rs4641528) and F 5' -CCC AAG TCA TAC TCG TGT TCA CTC AC-3' , R 5' -ACT CTT GTG TGC CAC TGC CAT CTA G-3' (rs10879355). The amplication mixture contained 1 μl of 100 ng/μl DNA, 5 μl of 10× PCR buffer, 1 μl of dNTP mixture, 2 μl primer, 27.75 μl distilled water, and 1.25 μl Taq polymerase (TaKara, Japan). The thermal cycling conditions were as follows: 95 ℃ for 15 min, followed by 35 cycles of 95 ℃ for 15 s, 62 ℃ for 20 s, 72 ℃ for 20 s, and ending with an extension step at 72 ℃ for 10 min (Thermal cycler 2720, Applied Bio-systems, Foster City, CA, USA).

4. Data collection

Collection of demographic and clinical data and assessment of PSD and PSEI were performed until February 2010. The

questionnaire for this study was given on the same day and administered by trained interviewers to increase the inter-rater reliability of the assessments.

At 3 months post stroke, the assessment for PSD and PSEI was conducted during out-patient clinic visits. The interviewer, interview procedure, and questionnaire were identical to those during the first interview (Choi-Kwon, 2012).

Briefly, data collection from first interview was summarized as follows. That was performed after the onset of stroke after the patients had stabilized (average of 4.7 days), thus avoiding any possible effects of acute neurological progression on patients' emotion. The majority of the interviews were conducted in the presence of the relatives, who confirmed the patients' responses. When the relatives were not present during the interview (n=17), the patients' responses were confirmed by calling the relatives who lived with the patients. The patients' modified Rankin scale (mRs) and neurological findings were recorded by one of the experienced stroke neurologists.

For the DNA analysis, whole-blood was drawn from all patients into EDTA-tubes and the plasma samples were isolated and then stored at -70 ℃ freezer previously using a QIAamp DNA mini Kit (Qiagen Inc, USA).

The institutional review board of Asan Medical Center approved this study. Written informed consent was obtained from all patients or their care givers after a detailed description of the study was given to them.

5. Data analysis

Details of the data analysis are as follows;

1) Descriptive statistics were used to summarize data.

2) The presence of the Hardy-Weinberg equilibrium was tested by the χ^2 test for goodness of fit.

3) Linkage disequilibrium (LD) was determined with the Haploview software program ver 3.32

(http://www.broad.mit.edu/mpg/haploview/).

4) Differences in demographics and clinical variables between the PSD and PSEI stroke patients and non PSD and PSEI stroke patients were evaluated with the by χ^2 test or Fisher's exact test.

5) Differences in genotype and allele frequencies between the PSD and PSEI stroke patients and non PSD and PSEI stroke patients were evaluated with the χ^2 test or Fisher's exact test.

6) Multiple logistic regression analysis was used to determine whether PSD and PSEI were influenced by the TPH2 gene after age, gender and factor were accounted for as covariates.

7) Statistical significance was defined at $p<.05$.

Ⅳ. Results

1. Characteristics of the patients

1) General characteristic of the subjects

The mean age of the stroke patients was 61.41 ± 12.38 years. Out of the 383 interviewees, 240 (63%) were men and 143(37%) were women. One hundred seventy-one (45%) patients graduated from middle school and 137(36%) were current cigarette smokers. Seventy nine (21%) patients consumed alcoholic drinks (Table 1).

<Table 1> General characteristic of the patients at 3 months post stroke (n=383)

Variables		n (%)
Age (years)		
	<64	205 (54%)
	65~74	130 (34%)
	>75	48 (13%)
Gender		

	Male	240 (63%)
	Female	143 (37%)
Educational level		
	< 9 years	171 (45%)
	10~12 years	99 (26%)
	>13 years	102 (27%)
	No response	11 (3%)
Smoking		
	Current	137 (36%)
	Ex-smoker	55 (14%)
	None	191 (50%)
Alcoholic intake		
	Yes	79 (21%)
	No	304 (79%)

2) Clinical characteristic of the subjects

The following is the result of vascular risk factors of the patients. Two hundred sixty seven (70%) patients had hypertension, 98 (26%) had diabetes, 295 (77%) had cardiovascular disease and 177 (46%) had hyperlipidemia. Of the total patients, 67 (17%) had a previous stroke and 115 (30%) patients had cortical lesions.

One hundred seventy (44%) patients had motor dysfunction, 141 (37%) had sensory dysfunction, 115 (30%) had dysarthria and 121 (32%) had ataxia. Based on the modified Rankin scale at admission, 30 (8%) patients had severe disability or dependence in the daily activities (Table 2).

The mean NIHSS score of the 383 patients was 3.92 $\pm$ 3.31 at admission and 2.58 $\pm$ 2.53 at discharge.

<Table 2> Clinical characteristic of the patients at 3 months post stroke (*n*=383)

Variables	*n*	(%)
Hypertension		
Yes	267	(70%)
Diabetes		
Yes	98	(26%)
Cardiovascular disease		
Yes	295	(77%)
Hyperlipidemia		
Yes	177	(46%)
Previous stroke		
Yes	67	(17%)
Lesion location		
Cortex	115	(30%)
Subcortex	114	(30%)
Cortex + Subcortex	31	(8%)
Medulla	26	(7%)
Pons + Midbrain	58	(15%)
Cerebellum	38	(10%)
Motor dysfunction		
Yes	170	(44%)
Sensory dysfunction		
Yes	141	(37%)
Dysarthria		
Yes	115	(30%)
Ataxia		
Yes	121	(32%)
No	247	(64%)
No response	15	(4%)
mRs at admmision		
Mild	353	(92%)
Severe	30	(8%)
mRs at 3 months		
Mild	358	(93%)
Severe	25	(7%)

3) Genetic characteristic of the subjects

In this study, we selected two tagging SNPs (rs10879355, rs4641528) covering the TPH2 gene. The frequencies of rs10879355 genotypes were C/C=25.8%, C/T= 52.5%, and T/T= 21.7% in our patients. The frequencies of rs4641528 genotypes were C/C=18.8%, C/T= 59.5%, and T/T= 21.7% in our patients (Table 3).

<Table 3> Genetic characteristic of the patients at 3 months post stroke (*n*=383)

SNP ID	*n*	Allele frequency (%)		Genotype frequency (%)		
rs10879355		C	T	C/C	C/T	T/T
All subjects	383	399(52.1)	367(47.9)	99(25.8)	201(52.5)	83(21.7)
Gender						
Male	240	242(50.4)	238(49.6)	54(22.5)	134(55.8)	52(21.7)
Female	143	157(54.9)	129(45.1)	45(31.5)	67(46.9)	31(21.7)
rs4641528		C	T	C/C	C/T	T/T
All subjects	383	372(48.6)	394(51.4)	72(18.8)	228(59.5)	83(21.7)
Gender						
Male	240	234(48.8)	246(51.3)	45(18.8)	144(60.0)	51(21.3)
Female	143	138(48.3)	148(51.7)	27(18.9)	84(58.7)	32(22.4)

2. Prevalence of PSD and PSEI at 3 months post stroke

There were 69 (18%) PSD patients and 42 (11%) PSEI patients at 3 months after stroke (Table 4).

<Table 4> PSD and PSEI in the patients at 3 months post stroke (n=383)

Variables		n (%)
PSD		
	Yes	69 (18%)
	No	314 (82%)
PSEI		
	Yes	41 (11%)
	No	342 (89%)

3. Factors associated with PSD and PSEI

1) Genotype and allele frequency of TPH2 SNPs

Genotype frequencies for rs10879355 in stroke patients without PSD and PSEI were in Hardy-Weinberg Equilibrium (HWE) (p>.05). However, the genotype frequencies for rs4641528 were not in HWE (p>.05). Linkage disequilibrium (LD) estimates (D′) between the SNPs were .69 in the patients.

No differences in the allele frequencies of the TPH2 SNPs (rs10879355 and rs4641528) were observed between PSD and PSEI and non PSD and PSEI patients. However, the genotype frequencies of rs4641528 differed significantly 3 months post stroke between the patients with and without PSD and PSEI (Table 5). In SNPs combination type analysis, we also found no significant differences between the PSD and PSEI and non PSD and PSEI groups (Table 6).

<Table 5> Genotype and allele frequencies in PSD and PSEI at 3 months post stroke

SNP ID	n	Allele frequency (%)		p	Genotype frequency (%)			p
rs10879355		C	T		C/C	C/T	T/T	
PSD								
No	314	333(53.0)	295(47.0)	.301	86(27.4)	161(51.3)	67(21.3)	.338

Yes	69	66(47.8)	72(52.2)		13(18.8)	40(58.0)	16(23.2)	
PSEI								
No	342	356(52.0)	328(48.0)	.946	89(26.0)	178(52.0)	75(21.9)	.882
Yes	41	43(52.4)	39(47.6)		10(24.4)	23(56.1)	8(19.5)	
rs4641528		C	T		C/C	C/T	T/T	
PSD								
No	314	299(47.6)	329(52.4)	.301	61(19.4)	177(56.4)	76(24.2)	.015
Yes	69	73(52.9)	65(47.1)		11(15.9)	51(73.9)	7(10.1)	
PSEI								
No	342	327(47.8)	357(52.2)	.244	65(19.0)	197(57.6)	80(23.4)	.040
Yes	41	45(54.9)	37(45.1)		7(17.1)	31(75.6)	3(7.3)	

<Table 6> Combination type frequencies in two SNPs of TPH2 at 3 months post stroke

rs10879355	rs4641528	Frequency (%)	
		PSD	PSEI
C	C	2 (16.7)	0 (.0)
C	T	14 (19.7)	8 (11.3)
T	C	5 (7.0)	3 (4.2)
T	T	48 (21.0)	30 (13.1)
Global *p*-Value		.358	.291

2) The factors associated with PSD and PSEI

As shown in Table 7, PSD was not associated with gender, hypertension, diabetes, hyperlipidemia, previous stroke and lesion location. However, educational level (p<.05), motor dysfunction (p<.05), sensory dysfunction (p<.05), dysarthria (p<.01), high NIHSS score at admission (p<.01), mAs at admission (p<.05) and mAs after 3 months (p<.01) were

significantly associated with PSD 3 months post stroke.

There were no significant differences in age, gender, educational level, hypertension, cardiovascular disease, hyperlipidemia, previous stroke, functional level, NIHSS score and mRs at admission between patients with PSEI and those without. Lesion location (p<.05) and mRs at 3 months (p<.05) were associated with PSEI at the 3 months follow-up.

<Table 7> Factors associated with PSD and PSEI at 3 months post stroke

Variable		PSD		PSEI	
		Present (n=69)	Absent (n=314)	Present (n=41)	Absent (n=342)
Age(years ± *SD*)		62.94ears ±	61.07ears F	59.73ears	61.61ears F
Gender					
	Male	37(53.6)	203(64.6)	26(63.4)	214(62.6)
Years of education (years ± *SD*)		9.08rs ± e	10.48s ± e	10.82 of e	10.18 of e
Hypertension					
	Yes	50(72.5)	217(69.1)	28(68.3)	239(69.9)
Diabetes					
	Yes	17(24.6)	81(25.8)	11(26.8)	87(25.4)
Cardiovescular disease					
	Yes	17(24.6)	71(22.6)	8(19.5)	80(23.4)
Hyperlipidemia					
	Yes	27(39.1)	150(47.8)	17(41.5)	160(46.8)
Previous stroke					
	Yes	10(14.5)	57(18.2)	7(17.1)	60(17.5)
Lesion location	Cortex	18(26.1)	97(30.9)	10(24.4)*	105(30.7)
	Subcortex	28(40.6)	86(27.4)	15(36.6)*	99(28.9)
	Cortex+Subcortex	4(5.8)	28(8.9)	1(2.4)*	31(9.1)
	Medulla	6(8.7)	20(6.4)	2(4.9)*	24(7.0)
	Pons + Midbrain	7(10.1)	51(16.2)	12(29.3)*	46(13.5)
	Cerebellum	6(8.7)	32(10.2)	1(2.4)*	37(10.8)
Motor dysfunction					
	Yes	39(56.5)*	131(41.7)	22(53.7)	148(43.3)
Sensory dysfunction					
	Yes	34(49.3)*	107(34.1)	21(51.2)	120(35.1)

Dysarthria					
	Yes	30(43.5)**	85(27.1)	15(36.6)	100(29.2)
Ataxia					
	Yes	27(39.1)	94(29.9)	11(26.8)	110(32.2)
NIHSS adm (scores ± *SD*		5.45S adm (	3.58ores	5.83S adm ±	3.69S adm
mAs at admission					
	Yes	10(14.5)*	20(6.4)	2(4.9)	28(8.2)
mAs at 3 months					
	Yes	12(17.4)**	13(4.1)	7(17.1)*	18(5.3)

*p < .05, **p < .01

Logistic regression was used to identify the factors related to PSD and PSEI. Table 8 presents the results of multiple logistic backward stepwise regression analysis for PSD and PSEI. We used significance level < 0.05.

In the analysis, we included age, gender, and factors significant in univariate analysis (p<.05). NIHSS and mAs at admission were included in place of individual neurological deficits due to the overlap. We found that the NIHSS score (p=.003) and mAs at 3 months (p=.019) were associated with PSD and rs4641528 (TPH2 SNPs) (p=.023) and the NIHSS score (p=.002) were associated with PSEI (Table 8).

<Table 8> Factors associated with PSD and PSEI at 3 months post stroke on multiple logistic regression analysis

Variable			*B*	*S.E.*	*p*	Exp(B)
PSD						
	NIHSS at admission	(Scores ± SD)	.123	.041	.003	1.131
	mAs at 3 months	Severe	1.181	.506	.019	3.259
	Constant		-3.454	.578	.000	.032
PSEI						
	rs4641528	C/C	1.180	.861	.170	3.255
		C/T	1.706	.752	.023	5.506
		T/T			.058	
	NIHSS at admission	(Scores ± SD)	.154	.049	.002	1.166
	Constant		-4.352	.769	.000	.013

V. Discussion

PSD and PSEI are thought to be developed by a complex interaction of important genetic and non-genetic contributing factors. Thus, this study examined their relationships between demographic, clinical, and genetic factors and emotional disturbances including PSD and PSEI at 3 months post stroke.

In the present study, 18% of our patients had PSD and 11% had PSEI at 3 months post stroke. These rates are slightly lower than those reported in previous studies (Astrom, 1996; Jong S Kim & Choi-Kwon, 2000). Differences in prevalence of PSD and PSEI are likely to be a result of differences in the timing of the assessment. We investigated PSD and PSEI in subacute stage. Some studies have noted a decline in the incidence and prevalence of emotional disturbance over time (N. Herrmann et al., 1998). Psychosocial-behavioral intervention may reduce emotional disturbances during the subacute stage of stroke (Michell et el., 2009).

A time frame of 3 months was chosen for this study, as this is the time when the majority of stroke survivors will have been or are nearing discharge into the community (Barker-Collo, 2007). In addition, depression in acute recovery from brain injury is related to the site of injury, while delayed onset depression is linked to psychological mechanisms (Astrom, 1996). Specifically, acute PSD is related to left hemisphere lesion, but this relationship disappears at, or beyond, 3 months post injury (Bhogal, Teasell, Foley, & Speechley, 2004)

The factors related to each type of emotional disturbance differed although we found that PSD and PSEI were closely associated. Significant correlates of PSD at 3 months later in present study were education level, functional level (motor dysfunction, sensory dysfunction, and dysarthria), features of the index stroke (mAs), and stroke severity based on NIHSS score. The importance of functional level has been noted by other investigators (G. Andersen, Vestergaard, Ingemann Nielsen, & Lauritzen, 1995; Gottlieb, Salagnik, Kipnis, & Brill, 2002; N. Herrmann, S. Black, J. Lawrence, C. Szekely, & J. Szalai, 1998). The lack of relationship between PSD and lesion location is consistent with the studies of Fuentes et el., (2009).

In previous studies regarding PSEI, however, lesion location was the most important factor determining PSEI (Jong S

Kim, 2002). Likewise, one of the determinants of PSEI at 3 months after stroke was the lesion location in the present study. Our data are in agreement with a recent PET study, in which the brain of patients with post stroke pathologic crying had low baseline serotonin binding potentials (M ¤ ller, Andersen, & Gjedde, 2007). Moreover,, NIHSS score and mAs at 3 months were closely associated with PSEI. This suggest that PSEI is affected by the lesion location itself as neurotransmitter among other things and PSD occurs because of due to the social, psychological, and physiological stresses associated with stroke.

In the SNP evaluation, we found a statistically significant association of SNP rs4641528 with PSD and PSEI at 3 months. However, there was no difference in the genotype and allele frequencies of rs10879355 between the patients with PSD and PSEI and those without. Also, we failed to verify the hypothesis that combination type in two SNPs has a correlation with PSD and PSEI. The result suggests that SNP rs4641528 may have an effect on post stroke emotional disturbance unlike SNP rs10879355 and combination type did.

Our finding supports the hypothesis that a genetic variation in TPH2 gene may be associated with PSD and PSEI. The frequency of C/T (heterozygous) genotype of TPH2 was higher in PSD and PSEI. The TPH gene is a promising candidate for post stroke emotional disturbance since it is a rate-limiting enzyme of serotonin synthesis. The recent identification of the new TPH2 isoform offers now new possibilities in the study of PSD and PSEI, disorders with disturbances in the serotonergic system, and provides further clinical implications (Lim, Pinsonneault, Sadee, & Saffen, 2007). Multiple logistic regression results indicated that severe mAs at 3 months and high NIHSS were determinants of PSD. For PSEI, rs4641528 genotype (C/T) and high NIHSS were independent predictors. We therefore recognize contributions from both genetic factors and physical dysfunction interacting in the development of emotional incontinence at 3 months post stroke.

There are some limitations in the present study. We investigated two SNPs. Two SNPs can only provide a partial insight into the genetic basis of complex disorders such as PSD and PSEI. Besides, genotype frequencies were in Hardy-Weinberg equilibrium for rs10879355, however not for rs4641528. The subjects of this study consists of only the case group but not the case-control groups Selection, in general, cause allele frequencies to change, often quite rapidly. While directional

selection, only patients group without control group, eventually leads to the loss of all allele except the favored one, some forms of selection, such as balancing selection, lead to equilibrium without loss of alleles. Further study is needed adjusted for HWE deviation. Adjustment for deviation from HWE improved the significance (Zintzaras, 2010). Finally many neurobiological systems might be involved in the prevalence of PSD and PSEI. Not only the serotonergic system, but also the dopaminergic and adrenergic systems may also be implicated. Both hormonal and immunologic systems can be involved, and they all interact with each other. Thus, these interactions can act as confounding factors, making it very difficult to interpret the effect of only one factor. Nevertheless, our results showed that other risk factors may be involved, including biological, physical, and functional disability, as well as the genetic factors in the development of PSD and PSEI.

VI. Conclusion

Our study is the first to characterize an association of TPH2 polymorphisms with PSD and PSEI in Korean stroke patients. Our results suggested that rs4641528, one of the TPH2 SNPs, may have an important effect on PSD and PSEI at 3 months post stroke. Moreover, the results of this study suggest that PSD and PSEI are commonly experienced 3 months post stroke. In present study, significant correlates of PSD at 3 months post stroke were education level, functional level (motor dysfunction, sensory dysfunction, and dysarthria), features of the index stroke (mRs), and stroke severity . Lesion location and high NIHSS may be linked to PSEI at 3 months post stroke.

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국문초록

뇌졸중 환자는 질병의 특성상 급성기를 넘기고 생존하여도 다양한 만성 장애가 동반되며, 특히 빈번하게 발생하는 뇌졸중 후 우울 (Post stroke depression)과 뇌졸중 후 감정조절장애 (Post stroke incontinence) 와 같은 뇌졸중 후 감정장애는 환자의 삶의 질을 저하시키고 사망률을 증가하는 큰 요인으로 보고되고 있다. 또한 가족 간호자의 부담감을 증가시키며 이는 환자의 재활에 부정적인 영향을 미칠 수 있다. 이에 뇌졸중 후 환자의 우울 (PSD) 및 감정조절장애 (PSEI)의 관련 요인에 대한 이해가 필요하다.

본 연구는 뇌졸중 발생 후 3개월에, 환자의 일반적, 임상적, 유전적 특성을 알아보고, 뇌졸중 후 우울과 감정조절정애에 미치는 요인을 파악하고자 한다. 특히 뇌졸중 후 우울과 감정조절장애가 TPH2 유전체 다형성과 관련 있는지 규명하여 뇌졸중 후 환자에게 제공되는 간호의 과학적 기초 자료를 제공하기 위한 서술적 조사연구이다.

연구 대상은 서울시내 일개 종합병원에서 뇌졸중으로 진단 받은 후 3개월 후 외래 진료를 받고 있는 환자 383명이었다. 2008년 3월부터 2010년 2월까지 연구에 참여하기로 동의한 환자에게 설문지와 유전학적 검사를 시행하였다. 자료 수집은 해당 병원의 연구대상자보호 심의위원회를 통과한 후 시작하였다.

연구 도구로 뇌졸중 후 우울은 Beck depression Inventory (BDI)를, 뇌졸중 후 감정조절장애는 김종성의 진단 기준을 이용하였다.

수집한 자료의 분석은 SPSS 21.0 통계 분석 프로그램을 이용하여 빈도, 백분율, 평균, 표준편차, χ^2-test, Fisher's exact test, 단계별 다중회귀분석 방법으로 분석하였다.

연구 결과는 다음과 같다

1) 본 연구에서 뇌졸중 후 우울은 18% (69명), 뇌졸중 후 감정조절장애는 11% (41명) 발생하였다.

2) TPH2 단일염기다형성 중 rs10879355는 뇌졸중 후 감정장애와 유의한 차이가 없었으나, rs4641528은 뇌졸중 후 우울 (p=.015), 뇌졸중 후 감정조절장애 (p=.040)와 통계적으로 유의한 차이가 있었다.

3) 뇌졸중 후 우울은 운동장애 (p<.05), 감각장애 (p<.05), 구음장애 (p<.01), 입원시 NIHSS score (p<.01), 입원시 mRs (p<.05), 3개월 후 mRs (p<.01)에 따라서 통계적으로 유의한 차이가 있었다.

4) 뇌졸중 후 감정조절장애는 뇌병변 위치 (p<.05), 입원시 NIHSS score (p<.01), 3개월 후 mRs (p<.05)에 따라서 통계적으로 유의한 차이가 있었다.

5) 성별, 나이, 유의한 변수로 단계별 다중회귀분석을 실시한 결과 입원시 NIHSS score (β=.123)와 3개월 후 mRs (β=1.181)

변수가 뇌졸중 후 우울에 영향을 미치는 요인임이 규명되었다.

6) 성별, 나이, 유의한 변수로 단계별 다중회귀분석을 실시한 결과 TPH2 단일염기다형성인 rs4641528 (β=1.706)과 입원시 NIHSS score (β=.154) 변수가 뇌졸중 후 감정조절장애에 영향을 미치는 요인임이 규명되었다.

본 연구는 뇌졸중 후 3개월 된 환자에서, 뇌졸중 후 우울과 감정조절장애 유병률을 파악하였고 뇌졸중 후 우울과 감정조절장애에 영향을 미치는 요인을 규명하였다. 특히 일반적, 임상적 요인과 더불어 유전학적 요인인 TPH2 유전체 다형성과 관련성을 파악하였다. 따라서, 이 연구의 결과는 뇌졸중 후 환자에게 제공되는 간호의 과학적 근거를 제시할 수 있으며, 나아가 이를 기초로 간호의 질 향상에 기여할 수 있을 것이다.

주요어 : 뇌졸중, 뇌졸중 후 우울, 뇌졸중 후 감정조절장애, TPH2 다형성

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